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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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FOLEY AND LARDNER LLP
SUITE 500
3000 K STREET NW
WASHINGTON, DC 20007

EXAMINER	
RAMACHANDRAN, UMAMAHESWARI	
ART UNIT	PAPER NUMBER
1617	
MAIL DATE	DELIVERY MODE
08/23/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/734,640	LIGNIERES ET AL.	
	Examiner	Art Unit	
	Umamaheswari Ramachandran	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 June 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4 and 6-14* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4 and 6-14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The examiner notes the receipt of the amendments and remarks received in the office on 6/12/2007 amending claim 1, canceling claim 5 and adding claims 12-14. The examiner acknowledges the substitute Oath/Declaration by the Applicant identifying the citizenship, mailing address, city, state or country of residence. The examiner notes the receipt of the declaration under 37 CFR 1.132 filed 6/12/2007 to overcome the rejection of claims 1-11 under U.S.C. 103. Claims 1-4, 6-14 are pending.

Response to Remarks

Applicant's arguments filed 6/12/2007 regarding 35 U.S.C 103 rejections of claims 1-11 have been fully considered but they are not persuasive. Accordingly, the rejections of the claims 1-11 are being maintained. The limitations of additional new claims 12-14 fall within the scope of the rejected claims 1-11 and hence have been rejected under the same 35 U.S.C 103 rejections that was made in the previous office action (non-final rejection). In view of applicants' amendments and addition of new claims a modified 35 U.S.C 103(a) rejection is now made. Further examination and search necessitated the new ground(s) of rejection presented in this Office action. Thus the office action is made non-final.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-3, 6-8, 10, 11-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Jarvis (Current Therapy in Endocrinology and Metabolism, 280-284) in view of Pujol et al. (Cancer Chemother Pharmacol, 36, 493-498, 1995) and further in view of in view of Fentiman et al. (Br. J. Surg, 75, 845-846, 1988).

Jarvis teach studies have been performed to determine if 4-hydroxy tamoxifen, a very active metabolite of tamoxifen that has an affinity for the estrogen receptor 100 times greater than that of tamoxifen, can be used percutaneously to avoid the systemic effects of the oral administration of tamoxifen in benign breast disease. The reference further teaches the results from those studies that 4-hydroxy tamoxifen when topically applied in alcoholic solution over the human breast is absorbed through the skin and is retained. The reference teaches that tamoxifen has been proposed for the treatment of benign breast disease (one of the symptoms being breast pain (mastodynia or mastalgia) but due to drawback of its use in premenopausal women leading to an increase in gonadotropin secretion studies were performed with 4-hydroxy tamoxifen (p 281, col. 1, col. 2, Antiestrogens).

The reference does not teach the amount of 4-hydroxy tamoxifen in the percutaneous administration.

Pujol et al. teaches a percutaneous administration of 0.5 mg, 1.0 mg, 2.0 mg of 4-hydroxy tamoxifen in a hydroalcoholic gel to breast areas for the treatment of breast cancer (see Abstract, p 494, study design).

Jarvis and Pujol et al. do not teach mastalgia to be cyclical.

Fentiman teaches a method of treatment of mastalgia comprising oral administration of 10 or 20 mg of tamoxifen to patients with either cyclical or non-cyclical breast pain (see Abstract, p 845, col. 2, lines 10-12).

It would have been obvious to one of ordinary skill in the art at the time of the invention to administer 4-hydroxy tamoxifen at a dose of at least 1.5 mg/day or the dosages claimed in the instant invention. One of ordinary skill in the art would have been motivated to administer such claimed amounts of 4-hydroxy tamoxifen in the treatment of mastalgia because of expectation of success as Pujol et al. clearly teaches percutaneous administration of 4-OH-tamoxifen (0.5 mg and 1.0 mg/breast) to patients. The examiner respectfully points out the following from MPEP 2144.05: "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955); see also Peterson, 315 F.3d at 1330, 65 USPQ2d at 1382 ("The normal desire of scientists or artisans to improve upon what is already generally known provides the motivation to determine where in a disclosed set of percentage ranges is the optimum combination of percentages."); *In re Hoeschele*, 406 F.2d 1403, 160 USPQ 809 (CCPA 1969); Merck & Co. Inc. v. Biocraft Laboratories Inc., 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), cert. denied, 493 U.S. 975 (1989); *In re Kulling*, 897 F.2d 1147, 14 USPQ2d 1056 (Fed.Cir. 1990); and *In re Geisler*, 116 F.3d 1465, 43 USPQ2d 1362 (Fed. Cir. 1997). It would have been obvious to one of ordinary skill in the art to use 4-hydroxy tamoxifen in a method of treatment of cyclical mastalgia. One of ordinary skill in the art would have been motivated to use 4-hydroxy

tamoxifen in a method of treatment of cyclical mastalgia because of the teachings of Fentiman and Jarvis. Jarvis teach the use of 4-hydroxy tamoxifen in benign breast disease (mastalgia, which includes both cyclical and non-cyclical) and the advantages of using 4-hydroxy tamoxifen over tamoxifen and Fentiman teaches the use of tamoxifen in the treatment of both cyclical and non-cyclical breast pain. It would have been obvious to one of ordinary skill in the art to use 4-hydroxy tamoxifen for tamoxifen in the treatment of cyclical breast pain as Jarvis teaches the drawbacks of using tamoxifen and the advantages of 4-OH tamoxifen and it is well known in the art that 4-OH tamoxifen is an active metabolite of tamoxifen.

Claims 1-3, 6-8, 10, 11-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Jarvis et al. ("Hormonal Therapy of Benign Breast Disease," Senologie et Pathologie Mammaire.4eme Congres International, Paris 1-4 September 1986, pp. 128-132) in view of Pujol et al. (Cancer Chemother Pharmacol, 36, 493-498, 1995) and further in view of in view of Fentiman et al. (Br. J. Surg, 75, 845-846, 1988).

Jarvis et al. teach studies have been performed to determine if 4-hydroxy tamoxifen, a very active metabolite of tamoxifen that has an affinity for the estrogen receptor 100 times greater than that of tamoxifen, can be used percutaneously to avoid the systemic effects of the oral administration of tamoxifen in benign breast disease. The reference further teaches the results from those studies that 4-hydroxy tamoxifen when topically applied in alcoholic solution over the human breast is absorbed through the skin and is retained. The reference teaches that tamoxifen has been proposed for the treatment of benign breast disease (one of the symptoms being breast pain

(mastodynia or mastalgia) but due to drawback of its use in premenopausal women leading to an increase in gonadotropin secretion studies were performed with 4-hydroxy tamoxifen (p 129, 130, Therapeutic Alternatives, Antiestrogens).

The reference does not teach the amount of 4-hydroxy tamoxifen in the percutaneous administration.

Pujol et al. teaches a percutaneous administration of 0.5 mg, 1.0 mg, 2.0 mg of 4-hydroxy tamoxifen in a hydroalcoholic gel to breast areas for the treatment of breast cancer (see Abstract, p 494, study design).

Jarvis and Pujol et al. do not teach mastalgia to be cyclical.

Fentiman teaches a method of treatment of mastalgia comprising oral administration of 10 or 20 mg of tamoxifen to patients with either cyclical or non-cyclical breast pain (see Abstract, p 845, col. 2, lines 10-12).

It would have been obvious to one of ordinary skill in the art at the time of the invention to administer 4-hydroxy tamoxifen at a dose of at least 1.5 mg/day or the dosages claimed in the instant invention. One of ordinary skill in the art would have been motivated to administer such claimed amounts of 4-hydroxy tamoxifen in the treatment of mastalgia because of expectation of success as Pujol et al. clearly teaches percutaneous administration of 4-OH-tamoxifen (0.5 mg and 1.0 mg/breast) to patients. The examiner respectfully points out the following from MPEP 2144.05: "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." I*n re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955); see also Peterson, 315 F.3d at 1330, 65

USPQ2d at 1382 ("The normal desire of scientists or artisans to improve upon what is already generally known provides the motivation to determine where in a disclosed set of percentage ranges is the optimum combination of percentages."); *In re Hoeschele*, 406 F.2d 1403, 160 USPQ 809 (CCPA 1969); Merck & Co. Inc. v. Biocraft Laboratories Inc., 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), cert. denied, 493 U.S. 975 (1989); *In re Kulling*, 897 F.2d 1147, 14 USPQ2d 1056 (Fed.Cir. 1990); and *In re Geisler*, 116 F.3d 1465, 43 USPQ2d 1362 (Fed. Cir. 1997). It would have been obvious to one of ordinary skill in the art to use 4-hydroxy tamoxifen in a method of treatment of cyclical mastalgia. One of ordinary skill in the art would have been motivated to use 4-hydroxy tamoxifen in a method of treatment of cyclical mastalgia because of the teachings of Fentiman and Jarvis. Jarvis teach the use of 4-hydroxy tamoxifen in benign breast disease (mastalgia, which includes both cyclical and non-cyclical) and the advantages of using 4-hydroxy tamoxifen over tamoxifen and Fentiman teaches the use of tamoxifen in the treatment of both cyclical and non-cyclical breast pain. It would have been obvious to one of ordinary skill in the art to use 4-hydroxy tamoxifen for tamoxifen in the treatment of cyclical breast pain as Jarvis teaches the drawbacks of using tamoxifen and the advantages of 4-OH tamoxifen and it is well known in the art that 4-OH tamoxifen is an active metabolite of tamoxifen.

Claims 1-3, 6-8, 10,11-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pujol et al. (Cancer Chemother Pharmacol, 36, 493-498, 1995) in view of Fentiman et al. (Br. J. Surg, 75, 845-846, 1988).

Pujol et al. teaches a percutaneous administration of 0.5 mg, 1.0 mg, 2.0 mg of 4-hydroxy tamoxifen in a hydroalcoholic gel to breast areas for the treatment of breast cancer (see Abstract, p 494, study design). The reference further teaches that 4-hydroxy tamoxifen is an active metabolite of tamoxifen (p 497, col. 1, line 18). Pujol et al. do not explicitly teach 4-hydroxy tamoxifen to be a racemic mixture but it is obvious that the compound has both the cis and trans isomers.

The reference does not teach 4-hydroxy tamoxifen in the treatment of mastalgia.

Fentiman teaches a method of treatment of mastalgia comprising oral administration of 10 or 20 mg of tamoxifen to patients with either cyclical or non-cyclical breast pain (see Abstract, p 845, col. 2, lines 10-12).

It would have been obvious to one of ordinary skill in the art at the time of the invention to use 4-hydroxy tamoxifen in the treatment of mastalgia. The motivation to do so is provided by Pujol et al. The reference teaches that 4-OH-tamoxifen is an active metabolite of tamoxifen and has 100-1000 fold stronger affinity to estrogen receptors compared to tamoxifen and the reference further teaches 4-OH-tamoxifen to be one of the most potent anti-estrogens and the compound penetrates through the skin. The reference also teaches that 4-OH-tamoxifen gel administration is associated with low systemic effects yet induces moderate breast tissue concentration.

Fentiman et al. and Pujol et al. do not teach administration of 0.75mg/breast of 4-OH-tamoxifen or a dose of 1.5 mg/day to patients but Pujol teaches administration of 4-OH-tamoxifen (0.5 mg and 1.0 mg/breast) to patients.

The examiner respectfully points out the following from MPEP 2144.05: "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." I*n re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955); see also Peterson, 315 F.3d at 1330, 65 USPQ2d at 1382 ("The normal desire of scientists or artisans to improve upon what is already generally known provides the motivation to determine where in a disclosed set of percentage ranges is the optimum combination of percentages."); *In re Hoeschele*, 406 F.2d 1403, 160 USPQ 809 (CCPA 1969); Merck & Co. Inc. v. Biocraft Laboratories Inc., 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), cert. denied, 493 U.S. 975 (1989); *In re Kulling*, 897 F.2d 1147, 14 USPQ2d 1056 (Fed.Cir. 1990); and *In re Geisler*, 116 F.3d 1465, 43 USPQ2d 1362 (Fed. Cir. 1997).

Claim 9 is rejected under 35 U.S.C. 103(a) as being unpatentable over Pujol et al. (Cancer Chemother Pharmacol, 36, 493-498, 1995) in view of Fentiman et al. (Br. J. Surg, 75, 845-846, 1988) as applied to claims 1-3, 6-8, 10, 11-14 above and further in view of Kochinke et al. (U.S. 5,613,958).

The teachings of Pujol et al. (Cancer Chemother Pharmacol, 36, 493-498, 1995) in view of Fentiman et al. (Br. J. Surg, 75, 845-846, 1988) have been discussed in the 103(a) rejection set forth above.

Pujol et al. and Fentiman et al. do not teach the hydroalcoholic gel comprising ethanol, isopropyl myristate and hydroxypropyl cellulose.

Kochinke et al. teaches a transdermal drug delivery system comprising a drug, plasticizer-type enhancer such as isopropyl myristate, a solvent-type enhancer such as

ethanol and a gelling agent such as hydroxypropyl cellulose (col. 9, lines 23-25, 47-59, col. 11, lines 6-25).

It would have been obvious to one of ordinary skill in the art to use a combination of isopropyl myristate, ethanol, and hydroxypropyl cellulose as a hydroalcoholic gel solution in the percutaneous delivery of 4-OH tamoxifen. The motivation to do so is provided by Kochinke et al. The reference teaches that solvent-type enhancer such as ethanol provide higher flux rate, plasticizer-type enhancer such as isopropyl myristate is used in combination with a solvent-type enhancer to deliver drugs through stratum corneum at therapeutically effective levels and to eliminate the irritation that occurs when solvent-type enhancers are used alone at high concentrations. In addition the reference teaches that a gelling agent such as hydroxypropylcellulose is added to increase the viscosity and rheological characteristics of the drug and enhancers.

Claim 4 is rejected under 35 U.S.C. 103(a) as being unpatentable over Pujol et al. (Cancer Chemother Pharmacol, 36, 493-498, 1995) in view of Fentiman et al. (Br. J. Surg, 75, 845-846, 1988) as applied to claims 1-3, 6-8, 10, 11-14 above and further in view of Malet et al (Cancer Research, 48, 7193-7199, 1988).

The teachings of Fentiman et al. (Br. J. Surg, 75, 845-846, 1988) in view of Pujol et al. (Cancer Chemother Pharmacol, 36, 493-498, 1995) have been discussed in the 103(a) rejection set forth above.

Pujol et al. and Fentiman et al. do not teach percutaneous administration of trans 4-hydroxy tamoxifen in the treatment of mastalgia.

Malet teaches percutaneous administration of trans 4-hydroxy tamoxifen to human breast of patients (see Abstract). The reference further teaches that trans-4-hydroxy tamoxifen is a very active metabolite of tamoxifen.

It would have been obvious to one of ordinary skill in the art to use trans 4-hydroxy tamoxifen for the treatment of mastalgia. The motivation to do so is provided by Malet et al. The reference teaches that trans-4-hydroxy tamoxifen is a very active metabolite of tamoxifen. The reference further teaches that cis-4-hydroxy tamoxifen exerts a potent estrogenic agonistic effect and a percutaneous administration of trans 4-hydroxy tamoxifen could produce a strong antiestrogenic effect at the molecular level.

Response to Arguments

The declaration under 37 CFR 1.132 filed 6/12/2007 is insufficient to overcome the rejection of claims 1-3, 5-8, 10,11 under 35 U.S.C. 103(a) as being unpatentable over Fentiman et al. (Br. J. Surg, 75, 845-846, 1988) in view of Pujol et al. (Cancer Chemother Pharmacol, 36, 493-498, 1995).

Applicants' argue that 4-hydroxy tamoxifen and tamoxifen are different compounds with distinct biological properties and effects and have different modes of action and the prior art do not provide a reasonable basis that 4-hydroxy tamoxifen would be useful in the therapeutic treatment of mastalgia. In response, it is well known in the art that 4-hydroxy tamoxifen is an active metabolite of tamoxifen. The prior art, Jarvis (Current Therapy in Endocrinology and Metabolism, 280-284) and Jarvis et al. ("Hormonal Therapy of Benign Breast Disease," Senologie et Pathologie Mammaire.4eme Congres International, Paris 1-4 September 1986, pp. 128-132)

teaches the use of tamoxifen in the treatment of benign breast disease and the drawbacks associated in using the antiestrogen and further teaches the benefits of 4-hydroxy tamoxifen in the treatment. Hence the teachings clearly indicate that 4-hydroxy tamoxifen, an active metabolite of tamoxifen being useful for the treatment of benign breast disease. Hence one of ordinary skill in the art would have been motivated to administer 4-hydroxy tamoxifen for tamoxifen in he treatment of benign breast disease (mastalgia). Further, Applicants' argument and Dr. Fourcroy's declaration indicate that Wijayaratne *et al., Endocrinology* 140:5828-840 (1999) teach both tamoxifen and 4-hydroxy tamoxifen differ in their biological activities and have different effects on estrogen receptor conformation and hence have different modes of action. Wijayaratne *et al.,* only teach the differences among antiestrogens but do not show any comparative data between 4-hydroxy tamoxifen and tamoxifen showing the mechanistic differences between them and indicating that the active metabolite of tamoxifen, namely 4-hydroxy tamoxifen has a different mode of action than that of tamoxifen.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Umamaheswari Ramachandran whose telephone number is 571-272-9926. The examiner can normally be reached on M-F 8:30 AM - 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on 571-272-0629. The fax phone

number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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SREENI PADMANABHAN
SUPERVISORY PATENT EXAMINER